41 ~~105~~. (amended) The method according to claim [105] ~~104~~ 40 in which the stem and progenitor cells are autologous to the host.

42 ~~106~~. (amended) The method according to claim [105] ~~104~~ 40 in which the stem and progenitor cells are syngeneic to the host.

43 ~~107~~. (amended) The method according to claim [105] ~~104~~ 40 in which the stem and progenitor cells are allogeneic to the host.

44 ~~108~~. (amended) The method according to claim [108] ~~107~~ 43 in which the host has Fanconi's anemia.

45 ~~109~~. (amended) The method according to claim [105] ~~104~~ 40 in which the blood components are isolated by collection from an umbilical cord.

110. (amended) A method for treating a human patient <u>in need of hematopoietic stem cell function</u> [having a disease or disorder] comprising introducing into the patient a composition comprising human neonatal or fetal hematopoietic stem cells [derived] from the blood, in which the stem cells have been previously cryopreserved<u>, so as to provide hematopoietic stem cell function</u>.

REMARKS

Claims 60, 82 and 104-110 have been amended, to more particularly point out and distinctly claim the invention under 35 U.S.C. § 112, second paragraph. The amendments are fully supported in the application as filed. The amendments to claims 60, 82, 104 and 110 merely make it explicit that the patient is in need of hematopoietic stem cell function as discussed at the March 12, 1997 Examiner interview. As to the remaining amendments, they merely correct obvious clerical errors in claims 105-109, and delete the term "derived" as the Examiner had objected to this term as unclear in related applications.

1. Applicants' Interview Summary

Applicants take this opportunity to thank Examiner Stanton for conducting the interview on March 12, 1997 with Applicants' attorneys Adriane M. Antler and Nathan P. Letts. Applicants also would like to thank Supervisory Examiner Chambers for participating in and facilitating the interview.

In the interview, the section 103 rejection was discussed, as well as some of the amendments to the claims made hereinabove. The arguments for patentability advanced by Applicants' attorneys are substantially as set forth in this amendment.

2. Supplemental Information Disclosure Statement and Revised Form PTO-1449

Applicants are enclosing a Supplemental Information Disclosure Statement including a Revised Form PTO-1449, and enclosing and citing references including those cited in Oppositions filed in a related application granted before the European Patent Office and a related application accepted before the Japanese Patent Office. Applicants request that the that the Examiner indicate his consideration of these references on the Revised Form PTO-1449.

3. The Examiner's Rejection Under 35 U.S.C. § 101

On the bottom of page 2 of the January 22, 1997 Office Action, the Examiner provisionally rejected claim 60 under 35 U.S.C. § 101 as claiming the same invention as that of claim 60 of copending application Serial No. 08/443,221. The Examiner stated that this is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

In response, Applicants respectfully point out that claim 60 of U.S. Serial No. 08/443,221 has been canceled. Accordingly, the Examiner's rejection is moot.

4. The Examiner's Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 105-109 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner states that "[c]laims 105-109 are vague and indefinite because claim 105 depends from itself and claims 106, 107, and 109 depend from claim 105. Similarly, claim 108 depends from itself."

In response, Applicants have amended claims 105-109 to correct the obvious clerical errors, thus obviating the rejection. Furthermore, Applicants have amended claims 60, 82, 104 and 110 as discussed in the March 12, 1997 Examiner interview to more distinctly point out and claim what Applicants' regard as the invention.

5. The Examiner's Rejection Under 35 U.S.C. § 103

Claims 60-62, 67-102 and 104-111 are rejected under 35 U.S.C. § 103 as allegedly obvious. Specifically, the Examiner states that:

> Claims 60-62, 67-102 and 104-111 stand rejected under 35 U.S.C. § 103 as being unpatentable over Nakahata et al., 1982 (DX), Saunders, 1965 (AN) and either of Ende, 1966 (BV) or Ende et al., 1972 (BU), the preceding combination in view of Applicant's admissions on pages 10, 11, 27 and 28, Herzig et al., 1983 (CQ), McGlave et al., 1985 (DT) and Fabian et al., 1982 (BW) for reasons of record advanced in the preceding Office Action mailed 4/30/96 (Paper No. 6). Applicant's arguments filed 10/30/96 and 11/18/96 have been fully considered but they are not persuasive.
>
> Applicant reminds the examiner of the legal standard of obviousness in Paper No. 8 at pages 8 and 9. In response, it is noted that it is these standards that have been applied in the instant finding of obviousness.
>
> Applicant asserts that the examiner must have employed hindsight reasoning in the finding of obviousness. However, the instant invention is drawn to the use of a product which was known in the art to have been useful for the claimed purpose

and therefore the rationale supporting the instant grounds of obviousness was found in the prior art of record and is therefore not a result of hindsight reasoning.

Applicant summarizes that the claimed invention is drawn to hematopoietic reconstitution which requires long-term, complete reconstitution of the immune system *in vivo*. However, the pending claims are only drawn to methods of treatment rather than any long term reconstitution and the prior art of record as exemplified by Nakahata et al. indicates that fetal cord blood would have been expected to have comprised hematopoietic stem and progenitor cells similar to adult bone marrow. Since adult bone marrow was known to have been useful in the reconstitution of lethally irradiated subjects, the artisan, based upon the similarity between adult bone marrow and fetal cord blood, would have expected that fetal cord blood would have been useful in hematopoietic reconstitution as defined by applicant.

Applicant argues that none of the cited prior art indicates that one would have been motivated to have used cryopreserved blood in treatments of hematopoietic insufficiencies. However, no indication has been made that supports that cryopreserved blood is any different from any other type of blood.

Applicant argues that since fetal cord blood was often discarded that the artisan did not recognize its usefulness. However, Nakahata et al. indicates that the artisan was interested in fetal cord blood and recognized its properties.

Applicant argues that the teachings of the instant specification are required to have imputed a reasonable expectation of success in using human neonatal cord or fetal blood in treatments. However, the pending claims only require the use of such blood in a treatment and since such blood would, at a minimum, have been expected to have been useful as a blood replacement in, for example, infants, one would have reasonably expected it to have been useful in treatments. Further, Nakahata indicates that its composition would have included cells that would have made it more useful that circulating adult blood.

Applicant presents a number of arguments relating to the composition of fetal blood that one would not have recognized. In response, it is first noted that such properties would have been expected and secondly, even if such were not recognized, one would still have expected that blood, regardless of its source, would have been useful as part of a blood placement treatment regimen.

Applicant reviews the teachings of the prior art applied in the instant grounds of rejection and returns to the argument that one would not have reasonably expected hematopoietic reconstitution. However, it is reiterated that as pending the claims only require a treatment method rather than hematopoietic reconstitution. Further, while applicant characterizes the teaching of Nakahata as failing to disclose that stem cells are present in fetal cord blood, such is not a requirement for the artisan to have expected that a variety of hematopoietic lineages would have been reconstitutable using fetal cord blood as donor tissue. While neither the prior art nor applicant has demonstrated complete hematopoietic reconstitution of lethally irradiated hosts, such a demonstration is not necessary to support the instant

ground of rejection. First, one would have been motivated to have used any blood composition that contained greater proportions of hematopoietic progenitor cells and second it is impossible to prove "complete" hematopoietic reconstitution because the "complete" repertoire of the blood is undefined.

Applicant argues that the use of non-cryopreserved blood would not have motivated one to have used cryopreserved blood. However, cryopreservation was a known means of keeping cells viable for an extended period of time and therefore would have been expected to have been equivalent to noncryopreserved blood. In the absence of any indication of any material difference between cryopreserved and non-cryopreserved blood there is simply no way to distinguish the two compositions.

Applicant refers to a letter to the editor by Drs. Ende and Ende (see Paper No. 8, at pages 14 and 15) wherein it was indicated that umbilical cord blood had been used as early as 1972. However, such reference indicates that the potentiality of the use of cord blood was recognized. Applicant continues in the paragraph bridging pages 15 and 16, that in response to this letter to the editor, the editor, Dr. Gale, indicates a lack of expectation of success in using cord blood. However, in reviewing the entirety of the quotation in the latter paragraph of Paper No. 8, it is noted that Dr. Gale was referring to the use of non H.A. typed blood in combination with mild chemotherapy. After status the conditions, only then does Dr. Gale state "I would not expect engraftation to occur **under these conditions**...". Clearly, the conditions were critical to Dr. Gale's assessment of the transplantation using cord blood.

Applicant continues on page 16, first full paragraph of Paper No. 8, to indicate that disinterested third parties would only believe that cord blood would have been useful for temporary transfusion. However, even a temporary transfusion would be considered a treatment as required by the pending claims.

Applicant continues in the characterization of the teachings of the prior art on pages 16 and 17 by again indicating a failure of the prior art to indicate unequivocal complete hematopoietic reconstitution. However, such is not required for the claimed invention and has not been demonstrated in the instant application.

Applicant refers to the second Bernstein declaration which has been submitted as an unexecuted exhibit on 10/30/96 (Paper No. 9). In the reference and discussion of this declaration applicant points to the discussion in Paragraph 30 which relates to the expectation of the ability of fetal blood as an agent of long term hematopoietic reconstitution. In this discussion, a lack of relationship between adult bone marrow and fetal blood is advanced as is Bernstein's personal lack of expectation of the use of fetal blood as a long term reconstituting agent. However, no requirement for such reconstitution is required by the claimed invention.

Applicant argues that numerous sources evidence that different sources of stem cells were not considered equivalent or interchangeable. However, while the teachings presented by Applicant in Paper No. 8 at pages 20 and 21 support that

all stem cell sources were not identical, such teachings do not indicate that they are not all useful in various treatment regiments. While one source may be better than another, such differences were recognized in the art (as supported by applicants arguments) and support a finding that the artisan would have used any of a variety of hematopoietic cells in a variety of treatment regimens and would have been able to have determined which sources of hematopoietic stem/progenitor cells were appropriate for which treatment regimen.

Applicant refers to a reference by Thompson, 1995, entitled "Umbilical Cords: Turning Garbage Into Clinical Gold" and uses this reference to support the contention that one viewed umbilical cord blood as waste rather than a clinically useful treatment agent. However, reference to the cited article (reference IB) at the first and second paragraphs, deals predominantly with the recognition of the high number of CD34 positive cells representing early hematopoietic cells. While such advantages may have been recognized after the filing of the instant application, the artisan would have been motivated, at a minimum, to have used cord blood for other reasons and in other treatment modalities and therefore would have practiced what is claimed.

On pages 23 and 24 of Paper No. 8, applicant cites a number of references that indicate that one did not have appropriate assays to determine numbers of hematopoietic repopulating cells and that therefore one would not have had a reasonable expectation that one could have performed hematopoietic reconstitution. These arguments have been amply addressed above and it is reiterated that the invention as instantly claimed is not concordant with applicants apparent (although unsupported) assertion of unexpected results.

Applicant returns to the issue of the use of cryopreserved cells in the paragraph bridging pages 24 and 25 of Paper No. 8 and asserts that the teachings of the prior art disclosures used in the basis of the instant grounds are limited to the use of cryopreserved bone marrow cells and would not have been extendable to the use of cryopreserved fetal hematopoietic cells. Applicant further asserts that cells from different sources have different sensitivities to cryopreservation. In support of the latter assertion, applicant refers to articles relating to cryopreservation of liver cells (see Paper No. 8 at page 15). However, while it is granted that different cells have different sensitivities to freezing, the issue at hand is whether the same cells from a different source would have had a different sensitivity to freezing such that the artisan would not have expected them to have been useful once frozen. In this regard, applicant has not shown any material difference in the cells themselves that would have led the artisan to have had a less than reasonable expectation of success in using said cells once frozen.

Applicant continues beginning on page 25 of Paper No. 8 to address secondary considerations relating to a finding of obviousness. The first such consideration addressed relates to long felt need. In this regard, applicant indicates that a source of stem cells having properties associated with fetal issue has long been sought. However, such a need was had been addressed by various means such as autologous transplantation, use of identical twin donors, and the like. Since fetal tissue would have been expected to have been similar in many regards to the use

of adult bone marrow, the "need" addressed by the use of fetal tissue had been addressed in the prior art.

Applicant continues by reference to the second Bernstein declaration (Paper No. 9, attachment), which indicates that no wholly satisfactory alternative to the use of bone marrow had been found until the time of the instant application. However, no demonstration is of record that shows that the use of fetal blood was "wholly" satisfactory, thereby providing a solution as an ultimate blood donor tissue. While applicant continues on pages 29-33 by discussing the various disadvantages of the use of donor bone marrow, such advantages and disadvantages were recognized by the artisan, and no evidence or showing suggests that the use of fetal tissue "solves" all of these issues. Rather, the advantages detailed in the second Bernstein declaration as quoted in Paper No. 8 at page 33 and discussed on pages 34 and 35 are advantages that would have been recognized by the artisan since they are based upon the known properties of fetal tissue.

Beginning on page 36 of Paper No. 8, applicant characterizes the "Skepticism and Disbelief in the Art" as related to the use of fetal tissue. In this discussion which ensues on pages 38 through the top of page 48, details the teachings of a variety of pre- and post-filing references that relate to the advantages that are incumbent upon the use of fetal issue and the concordant use of such issue in a variety of hematopoietic reconstitution protocols. These teachings are not disputed. However, such "unexpected" results that would constitute evidence of non-obviousness need to be related to the invention as claimed. In the instant case, the claimed invention is drawn to a method of treatment. Applicants evidence suggests that the artisan was motivated to have used fetal blood in treatment modalities. The results and advantages as evidenced by applicant are, as a whole, drawn to hematopoietic reconstitution, which is not what is claimed. The artisan clearly expected to have been able to have "treated" patents with fetal issue whether or not they would have expected that they would have been able to have performed hematopoietic reconstitution.

Beginning on page 49 and extending through page 54 of Paper No. 8, applicant refers to an unexpected result relating to graft versus host disease. However, again, while such results may have been a result of an otherwise apparent and obviousness treatment, the claimed invention is not limited to such a result. The references to the expectation of success and the unexpected results only address a species of the broader genus currently claimed and without language limiting the chimed invention to such species of the claimed invention as argued as nonobvious by applicant, the invention as pending is maintained as being *prima facie* obvious due to its broad scope relating only to a general requirement as a treatment.

Applicant argues an improper use of hindsight reasoning because there was no reasonable expectation of success in performing hematopoietic reconstitution. However, again, the claims are not limited to such an invention.

For the foregoing reasons and based upon the scope of the pending claimed invention, it is therefore maintained that the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

A. Applicant's Invention.

Before discussing the specific issues raised in the January 22, 1997 Office Action, Applicants wish to briefly summarize their pioneering invention. Prior to Applicants' invention, human umbilical cords and the blood contained therein were considered a waste product. As described in the Thompson article (reference IB) entitled "Umbilical Cords: Turning Garbage Into Clinical Gold", what was once discarded has become valuable, indeed priceless, to many children with leukemia, all because of the teachings of the instant invention. Specifically, the article lists many advantages of using umbilical cord blood. One, it can be stored and can be transplanted back to its owner. Two, it can be donated to an unrelated recipient and has reduced immuno-reactivity and thus has reduced graft-versus-host disease (GVHD). Umbilical cord blood cells have a greater proliferative capacity than the same cells in bone marrow. Umbilical cord blood cells appear to be more susceptible to gene transplantation or gene therapy than bone marrow cells. Additionally, umbilical cord blood is readily available and is collected in a non-invasive manner, unlike bone marrow cells.

Applicants discovered that human umbilical cord blood contains sufficient stem cells to effect hematopoietic reconstitution in a human recipient. Stem cells are the most primitive cells in the hematopoietic lineage. Hematopoietic stem cells have extensive proliferative capacity and the ability to generate other stem cells as well as differentiate into progenitor cells, which in turn can differentiate into mature cells. The mature cells generated from human neonatal or fetal hematopoietic stem cells include cells from both the myeloid and lymphoid lineages. Applicants discovered that human umbilical cord contains sufficient human neonatal or fetal hematopoietic stem cells for use in treatment of patients in need of hematopoietic stem cell function. Based on this pioneering discovery, Applicants invented the methods defined by pending claims 60-62,

67-102 and 104-111. Using this pioneering discovery, Applicants and others have been able to treat many diseases. Hence the typically reserved and understated scientific press has headlines such as "Turning Garbage Into Clinical Gold" discussed above.

None of the cited references disclose a composition comprising a cryo-protective agent and human neonatal or fetal hematopoietic stem cells derived from blood. None of the cited references hint or suggest a method of treatment of a human patient in need of hematopoietic stem cell function which comprises administering such a composition. As will be discussed below, none of the references provide motivation to one of ordinary skill in the art to practice the invention defined by pending claims 60-62, 67-102, and 104-111. Moreover, even if there was some hint or suggestion to combine the cited references, which there is not, such a combination would not provide a reasonable expectation of success.

Specifically there are several reasons why there is no reasonable expectation of success for the claimed methods.

(1) knowledge common in the art regarding prior art sources of stem cells would, if anything, have led one to doubt the utility of the human neonatal or hematopoietic stem cells of the blood for use in treatment and for providing hematopoietic stem cell function (see the Second Bernstein Declaration);

(2) the presence of cells in cord blood which have the ability to generate colonies *in vitro*, before or after replating, does not reasonably predict the presence of stem cells capable of hematopoietic reconstitution (see the Second Bernstein Declaration ¶ 21);

(3) even assuming *arguendo* that stem cells with *in vivo* reconstituting ability were present, there is no teaching or expectation in the art that a collection of human neonatal/fetal blood cells that has been preserved from a single fetus would have

had a sufficient amount of stem cells to be therapeutically useful and to provide hematopoietic stem cell function; and

(4) concerned about maternal contamination and GVHD would have prevented a reasonable expectation of utility.

Lastly, the claimed invention exhibits several secondary indicia of nonobviousness, namely, the achievement of surprising results, the copying by others, and the fulfillment of a long-felt need.

B. The Shortcomings of Nakahata, et al.

Applicants discussed the Nakahata et al. reference (reference DX) in the Amendment filed October 30, 1996. Applicants incorporate by reference herein the discussions beginning on page 2 of that Amendment. Applicants also wish to point out the additional shortcomings of Nakahata et al. as described in the Second Bernstein Declaration. Specifically, on page 14, ¶ 20 of the Bernstein Declaration, he states:

> The presence of the cord blood cells detected by Nakahata et al. also does not reasonably predict the presence of the stem cell with the ability to effect hematopoietic reconstitution. Nakahata et al. discloses cord blood cells that are detected by their ability to produce, *in vitro*, after replating, multipotential colonies of hematopoietic cells including progenitors to colonies of granulocyte-erythrocyte-macrophage-megakaryocyte (GEMM) cells (Table II, p. 1327). However, no lymphoid colonies were identified (either before or after replating). Even Nakahata et al. note that "[w]e did not identify lymphoid colonies in the replating experiments of the blast cell colonies" (p. 1327, col. 2, first full paragraph.) The authors also state that "[t]his human blast cell colony may provide a method for quantitation of more primitive hematopoietic stem cells than progenitors for GEMM colonies (CFU-GEMM) in man," (p. 1324), and "[f]urther improvement of the replating conditions is necessary for confirmation of self-renewal capacity of human blast cell colonies" (p. 1328). As warranted by their data, nowhere in this publication do the authors suggest that their assay detects the stem cell with the ability to effect hematopoietic reconstitution. Nakahata et al. does not disclose cells which lead me, or would lead one of ordinary skill in the art, to reasonably expect that human neonatal or fetal blood contained the long-term marrow-repopulating stem cells so as to have utility for hematopoietic reconstitution.

Thus, the Second Bernstein Declaration shows that the claimed invention, namely, the claimed methods of providing hematopoietic stem cell function, is not hinted or suggested by Nakahata et al., alone or in combination with the other cited references. As discussed at length in the Amendment filed October 30, 1996, the other references cited by the Examiner do not remedy the deficiencies of Nakahata et al. (see Amendment filed October 30, 1996 at pages 12-17, incorporated by reference herein).

Briefly, Saunders et al. (reference AN) discloses a process for cryopreservation of blood, the use of mannitol as a cryopreservative, as well as the clinical transfusion of mannitolized blood. There is no disclosure or suggestion of the use of human neonatal or fetal blood.

Ende (reference BV) describes the administration of human umbilical cord blood to a patient with lymphangiosarcoma. The author states that the administration of cord blood was undertaken because such blood may contain factors which inhibit neoplasms. There is no cryopreservation of cord blood prior to transfusion, or any suggestion thereof. There is no evidence indicating the utility of cord blood for hematopoietic reconstitution or for providing stem cell function.

Ende et al. (reference BU) discloses mere transfusions using human cord blood. Ende et al. (BU) describes an attempted treatment of a patient with acute lymphoblastic leukemia by the transfusion of a total of eight human umbilical cord blood samples from different donors, over a period of 17 days. There was no cryopreservation of cord blood prior to transfusion. Ende et al. provides no reasonable basis for believing that any hematopoietic reconstitution was achieved or that any therapeutic effect was achieved which would motivate cryopreservation of a composition comprising cord blood stem cells or therapeutic use of such a cryopreserved composition.

Herzig (reference CQ) teaches bone marrow transplantation for hematopoietic reconstitution, including the use of cryopreserved bone marrow. Herzig also teaches that there are no suitable assays for the long-term marrow repopulating stem cells that effectuate hematopoietic reconstitution. Herzig discloses that *in vitro* colony assays of committed hematopoietic precursor cells "such as the granulocyte-macrophage colony-forming assay (CFU_c) or erythrocyte assays (. . . BFU_E; . . . CFU_E)" detect committed cells which differ from the pluripotent stem cell (p. 125). There is no hint or suggestion in Herzig of stem cells from human fetal or neonatal blood.

McGlave (reference DT) discloses allogeneic and autologous bone marrow transplantation for the treatment of a variety of disorders. GVHD is disclosed to be a major concern (pp. 180-189). There is no hint or suggestion of stem cells from human fetal or neonatal blood.

Fabian (reference BW) teaches cryopreservation of multipotential hematopoietic cells from human bone marrow. There is no hint or suggestion of stem cells from human fetal or neonatal blood.

C. Specific Allegations and Issues Raised in the January 22, 1997 Office Action.

To better define Applicants' invention under 35 U.S.C. § 112, Applicants have amended independent claims 60, 82, 104 and 110 to recite a method for treating a human patient in need of hematopoietic stem cell function. Applicants maintain that the amendment clarifies the intended purpose of the claimed invention, namely treatment by providing hematopoietic stem cell function. Addressing the specific issues raised in the January 22 Office Action, many of the Examiner's contentions are rendered moot in view of this clarification by amendment of the invention. Specific issues are addressed below.

Applicants note that on the bottom of page 3 the Examiner states "[t]he instant invention is drawn to the use of a product which was known in the art to be useful for the claimed purpose." Applicants respectfully disagree with the Examiner's contention.

Prior to Applicants' invention, a composition comprising a cryopreservative agent and human neonatal or fetal hematopoietic stem cells from the blood was not known. Thus, the product was not known in the art. Moreover, the therapeutic use of a composition comprising a cryoprotective agent and human neonatal or fetal hematopoietic stem cells was not known at the time of Applicants' effective filing date. Applicants point to the many papers mentioned on pages 36 to 47 of their October 30, 1996 Amendment Under 37 C.F.R. § 1.115 where they discuss skepticism and disbelief in the art. Such skepticism continued even after Applicants published papers describing their invention! In addition, in 1995, almost 8 years after Applicants' effective filing date, a paper such as "Umbilical Cords: Turning Garbage into Clinical Gold" (reference IB), evidences the fact that the invention was not known to have been useful for the claimed purpose. Thus, both of the Examiner's contentions regarding the product and the use of the product are mistaken.

In the paragraph bridging page 3 and page 4 of the January 22, 1997 Office Action, the Examiner states "the prior art of record is exemplified by Nakahata et al. indicates that fetal cord blood would have been expected to have comprised hematopoietic stem and progenitor cells similar to adult bone marrow". Here again, Applicants respectfully point out that the Examiner has misapprehended the claimed invention. As discussed above Nakahata et al. fails to disclose hematopoietic stem cells capable of generating the complete repertoire of mature blood cells, that is both myeloid and lymphoid cells. Moreover, the declaration of one skilled in the art, namely, the Second

Bernstein Declaration, shows that such a conclusion was not at all apparent from the Nakahata et al. reference. Accordingly, the Examiner's conclusory statement that Nakahata et al. discloses fetal cord blood contains stem cells similar to adult bone marrow is mistaken.

On the bottom of page 4 of the January 22, 1997 Office Action, the Examiner states "[i]t is reiterated that as pending the claims only require a treatment method rather than hematopoietic reconstitution." Here again, Applicants respectfully disagree with the Examiner. Applicants have amended independent claims 60, 82, 104 and 110 to recite a method for treating a human patient in need of hematopoietic stem cell function and "so as to provide hematopoietic stem cell function." Accordingly, Applicants' invention is directed to method and treatment which comprises administering cells capable of providing stem cell function such as for hematopoietic reconstitution.

In a similar vein, the Examiner states at the bottom of page 8 of the January 22, 1997 Office Action that "[t]he results and advantages as evidenced by applicant are, as a whole, drawn to hematopoietic reconstitution, which is not what is claimed". Here again, Applicants note that Applicants have amended independent claims 60, 82, 104 and 110 to recite the provision of stem cell function, to make them more clear. On the top of page 9, the Examiner makes a similar point again regarding the unexpected results related to GVHD. Applicants respectfully disagree with the Examiner's position. In fact, GVHD is a potential problem with transplants regardless of nature of the intended treatment. Nonetheless, Applicants have amended independent claims to recite a method for treating human patients in need of hematopoietic stem cell function. Accordingly, Applicants believe that in view of these amendments, this clarifies the invention and that the broad genus currently claimed exhibits the unexpected result.

On page 7 of the Office Action, the Examiner implies that Applicants' invention merely uses the same cells from different sources. Applicants disagree. The hematopoietic stem cells obtained from human neonatal/fetal blood are not only from a different source, but exhibit different properties than stem cells from other sources and thus are not identical to stem cells from other sources. Indeed, the fact that these different properties are unexpected further evidences the nonobviousness of the claimed invention.

A surprising property further distinguishing the invention defined by the pending claims and the cited references is the greater proliferative ability of human neonatal or fetal hematopoietic stem cells relative to bone marrow cells. Applicants point to Hao et al., Nov. 15, 1995, "A functional comparison of $CD34^+CD38^-$ cells in cord blood and bone marrow," Blood, 86(10):3745-53 (Exhibit 1 hereto). Hao et al. studied adult bone marrow and fetal cord blood to assess their relative proliferative abilities, specifically their ability to generate colony-forming unit cells. Hao et al. studied specific subpopulations of both bone marrow and umbilical cord blood. They found that one cord blood population of very primitive cells (a type of stem cell) ($CD34^+CD38^-$) had a higher cloning efficiency, proliferated more rapidly in response to cytokines, and generated "approximately sevenfold more progeny than [] their counterparts in bone marrow." Hao et al. abstract, page 3745. Hao et al. also found that the generative capacity of the more numerous $CD34^+CD38^+$ cells was more than twenty times that of their counterpart in bone marrow. See Hao et al., Table 2, page 3751. Accordingly, umbilical cord blood contains human neonatal or fetal hematopoietic stem cells that are certainly not equivalent to bone marrow cells. Moreover, the human neonatal or fetal hematopoietic stem cells have surprisingly greater proliferative ability.

Another difference between human neonatal or fetal hematopoietic stem

cells in bone marrow cells is the expression of the HLA-Dr antigen. The $CD34^+$ bone marrow cells that do not express the HLA-Dr antigen are enriched in more primitive stem cell-like progenitor cells. In contrast, in umbilical cord blood, i.e., human neonatal or fetal hematopoietic blood, the converse applies. That is, the more primitive cells express the HLA-Dr antigen. Hao et al. col. 1, page 3745. Here again, umbilical cord blood certainly is not the same as "other types of blood" and in fact shows very different and surprising results.

Furthermore, as discussed in the October 31, 1996 Amendment and as discussed in the Second Bernstein Declaration, the claimed methods unexpectedly offer lower GVHD, greater hematopoietic potential than those of bone marrow transplant methods, and provide cells that are more easily transducible than methods utilizing cells for other types of blood.

On page 8 of the January 22, 1997 Office Action, the Examiner contends that "no demonstration is of record that shows that the use of fetal blood was 'wholly' satisfactory, thereby providing a solution as an ultimate blood donor tissue" and that "[t]he advantages ... are advantages that would have been recognized by the artisan since they are based upon known properties of fetal tissue." In response, Applicants respectfully disagree, and point out that plentiful evidence of record demonstrates the fulfillment of long-felt needs by the present invention, and moreover point out that the Examiner is misapplying the legal standard since the invention need not be "wholly" satisfactory in order to do so. In fact, contrary to the Examiner's position, as described on pages 33-36 of the Applicants' October 30, 1996 Amendment and Exhibit A attached thereto, human neonatal or fetal hematopoietic blood stem cells do in fact fulfill the long-felt needs. Furthermore, subsequent to Applicants' filing, others have documented the uses of umbilical cord blood as a source for repopulating stem cells. Applicants point to

pages 34-41 of Exhibit A filed with Applicants' October 30, 1996 Amendment, which documents the fulfillment of long-felt needs. By way of example, Faulkner et al. in 1993 note that umbilical cord blood cells can successfully repopulate young patients with Fanconi's anemia or leukemia leading to sustained engraftment of donor cells. On page 35, Exhibit A describes Wagner 1994 which states that umbilical cord blood has been used to reconstitute the hematopoietic system of 34 patients with a variety of malignant and non-malignant diseases treated with myeloblative therapy, and states that adult cells may have latent viruses whereas umbilical cord blood is rarely contaminated. Moreover, Applicants disagree that the advantages of lower GVHD, greater hematopoietic potential, and greater transducibility were based upon known properties of fetal tissue. Applicants respectfully request that the Examiner support this assertion, *e.g.*, by an affidavit of personal knowledge under 37 CFR 1.107; on the contrary, such was unexpected. It was surprising that using human neonatal or fetal hematopoietic stem cells from the blood gave lower GVHD, that the contamination from maternal cells was not a problem, and that the volumes of blood obtainable from a single umbilical cord were sufficient to provide complete hematopoietic reconstitution. Moreover, these surprising results are amply supported by evidence of record, contrary to the Examiner's contention on page 7 of the Office Action (see Hao et al., Second Bernstein Declaration and the October 31 Amendment at pages 49-54).

On the bottom of page 4 of the January 22, 1997 Office Action, the Examiner states regarding previously unrecognized properties of the fetal blood composition that "[i]t is first noted that such properties would have been expected and secondly, even if such were not recognized, one would still have expected that blood, regardless of its source, would have been usable as part of blood placement treatment regimen."

In response, Applicants point out that the Examiner has provided no support whatsoever for his allegation that such properties would have been expected. In contrast, Applicants have provided the Second Bernstein Declaration which in ¶¶ 9-32 explains that one of ordinary skill in the art would not have predicted the presence of stem cells in cord blood capable of carrying out hematopoietic reconstitution. Specifically, Bernstein addresses the shortcomings of the Nakahata et al. disclosure. Furthermore, Applicants point again to papers such as "Umbilical Cords: Turning Garbage Into Clinical Gold" published years after Applicants' effective filing date. Thus, Applicants maintain that Nakahata et al., alone or in combination with any other reference cited by the Examiner, would not have led one of ordinary skill in the art to expect the properties asserted by Applicants to be unexpected, or to believe that cord blood could be used, with a reasonable expectation of success, for treating humans by providing hematopoietic stem cell function.

On the top paragraph of page 5 of the January 22, 1997 Office Action, the Examiner states "one would have been motivated to have used any blood composition that contained greater proportions of hematopoietic progenitor cells and second it is impossible to prove 'complete' hematopoietic reconstitution because the 'complete' repertoire of the blood is undefined".

In response, Applicants firstly respectfully point out that even assuming *arguendo* that the Examiner's allegation regarding motivation is correct, such is not the legal standard. The relevant point is that the cited art, even assuming *arguendo* that it suggested the use of any blood composition containing greater proportions of hematopoietic progenitor cells, did not provide a reasonable expectation of success in treatment by provision of stem cell function from human neonatal or fetal blood. Secondly, Applicants point out that it is well within the routine skill of one skilled in the

art to determine what would be indicative of a "complete" reconstitution. For example, the skilled artisan would look to reconstitution of both cells of the myeloid and lymphoid lineages. As described in the Second Bernstein Declaration, ¶9, cells of the myeloid lineage include erythroid cells, granulocytes, monocytes/macrophages and megakaryocytes; while cells of the lymphoid lineage include T-cells, B-cells, non-T cells and non-B cells. Note that Nakahata et al. assess and disclose that they did not identify any lymphoid colonies in replating experiments of the blast cell colonies. See Nakahata et al., p. 1327, col. 2.

Similarly, on the top of page 6 of the January 22, 1997 Office Action, the Examiner states that Applicants indicate "a failure of the prior art to indicate unequivocal complete hematopoietic reconstitution." In response, Applicants respectfully point out that the Examiner misconstrues Applicants' point. Rather, the point is that Nakahata et al. and the other cited prior art fail to give a reasonable expectation of success in achieving hematopoietic reconstitution or to provide hematopoietic stem cell function by the claimed methods. Also, Applicants respectfully submit that the Examiner is not applying the proper legal standard when he discusses on p. 5 of the Office Action Gale's description of the work of Ende and Ende. Specifically, regarding the Examiner's quote from Dr. Gale that "I would not expect engraftment to occur **under these conditions** ...", Dr. Gale is clearly referring to the conditions taught by Ende et al., upon which the Examiner relies in formulating the § 103 rejection. What Dr. Gale is saying is consistent with Applicants' position, namely, that one skilled in the art reading the Ende and Ende paper would not have a reasonable expectation of success, *i.e.*, would not expect engraftment or hematopoietic reconstitution to have taken place. Accordingly, the Ende and Ende paper (reference BU) does not provide one of ordinary skill in the art with a reasonable expectation of success to practice the invention defined by the pending claims.

On the bottom of page 5, the Examiner states that a "temporary transfusion would be considered a treatment as required by the pending claims." In response, Applicants point out that the claims as amended now recite a method of treating human patients by providing hematopoietic stem cell function; such function is not consistent with a temporary transfusion. Accordingly, the Examiner's position regarding temporary transfusions is moot.

In the second full paragraph on page 7 of the January 22, 1997 Office Action, the Examiner states "while it is granted that different cells have different sensitivities to freezing, the issue at hand is whether the **same** cells from a different source would have had a different sensitivity to freezing such that the artisan would not have expected them to have been useful once frozen". First, Applicants have presented evidence indicating that fetal liver cells are difficult to cryopreserve and that fetal liver cells have been substantially abandoned as a source of stem cells for hematopoietic reconstitution. Accordingly, one of ordinary skill if relying upon the properties of fetal tissue, would, if anything, have thought that fetal blood cells might share that property. Furthermore, as discussed above, stem cells prepared from different sources are not "the same." Specifically, as discussed above, adult bone marrow cells are not the same as neonatal or fetal hematopoietic cells. And as is now known, cryopreserved human neonatal/fetal stem cells of the blood have widespread utility for hematopoietic reconstitution in contrast to fetal liver stem cells. Moreover, the Examiner is using an incorrect legal standard. The proper issue is would one of ordinary skill in the art would have had a reasonable expectation of success for the claimed methods. Applicants maintain that there was no reasonable expectation of success for a method of treatment so as to provide stem cell function utilizing a cryoprotective agent and neonatal or fetal hematopoietic stem cells from the blood. In addition, Applicants wish to point out that,

as discussed in the Second Bernstein Declaration at ¶ 30, it was known in the art that adult peripheral blood or circulating blood under normal circumstances has few, if any, stem cells. Thus, human neonatal or fetal blood would not have been believed to be useful for provision of stem cell function, whether in cryopreserved form or not.

In the paragraph on the bottom of page 7 bridging page 8, the Examiner dismisses Applicants' exhaustively substantiated position regarding long-felt need. In fact, the Examiner is overlooking fifty pages summarizing over 74 references documenting the long-felt need for a source of stem cells having the properties associated with the claimed methods. As described on page 27 and page 28 of the October 30, 1996 Amendment, those skilled in art have long sought a source of stem cells capable of safely carrying out hematopoietic reconstitution, without problematic GVHD; with reduced potential for contamination by the patient's malignant themselves or having other diseases or disorders associated with adult patients or adult tissues; a source that is easily obtainable (without entailing an invasive surgical procedure and the attendant costs and risks); an inexpensive source; an abundance source; a widely available source; and a source not dependent on having a patient healthy enough to undergo a complicated procurement procedure. In fact, the invention defined by the methods provides these long sought after characteristics. Contrary to the Examiner's position, these needs were clearly not addressed by autologous transplantation or the use of identical twins. Autologous transplantation fulfills only one of these many long-sought needs (no problematic GVHD) while not fulfilling the others, as detailed in Exhibit A to the October 30, 1996 Amendment; and, clearly, very few people have identical twin donors!

In summary, Applicants maintain that they have demonstrated that the claimed methods provide surprising results not predicted by the art cited by the Examiner. Specifically, reduced host-versus-graft disease, reduced contamination, improved safety,

etc. They have demonstrated that nothing in the art would lead one to a reasonable expectation of success in the claimed methods of treatment of a patient in need of hematopoietic stem cell function. Furthermore, there are additional secondary considerations which have been described previously by Applicants, such as the long-felt need, the copying by others, and skepticism and disbelief in the art that further make the claimed methods non-obvious. Accordingly, Applicants respectfully request the Examiner reconsider and withdraw the rejection over 35 U.S.C. § 103.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the instant application. Withdrawal of the Examiner's rejections and allowance of the application is respectfully requested.

Applicants respectfully request that the Examiner call Adriane M. Antler at (212) 790-2247 if any questions or issues remain.

Respectfully submitted,

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